Kidney International, Vol. 4 (1973), p. 1–5

EDITORIAL

Chronic lead nephropathy

Granular contracted kidneys were recognized as regular features of chronic lead intoxication during the late nineteenth and early twentieth centuries [1–5]. At that time, however, increasing social consciousness resulted in legislation to define safe limits of lead exposure in industry and to control excessive lead absorption. Although the degree of control varied widely, the high standard of industrial hygiene in the most developed countries led to the virtual disappearance of the previously recognized renal complications of chronic lead intoxication [6–9]. Thus, a medical generation grew up that, never having seen severe industrial lead intoxication, doubted whether it was able to induce the previously recorded renal pathology. However, examples could still be found in less well developed countries [10, 11], although, because published descriptions were rarely in English, such reports tended to be overlooked. The latter part of the twentieth century has seen great emphasis upon the hazards of industrial pollution that has led to a reawakening of interest in the problem of the hazards of lead exposure [12], a more critical examination of the danger to humans from prolonged excessive absorption and storage of lead [13, 14] and determination of the maximum daily lead intake which is possible without the development of disease [15].

Because there were always a few cases of acute lead poisoning to be seen, and many of these showed a renal lesion by the presence of aminoaciduria and phosphaturia [16, 17], by cells in urine containing eosinophilic intranuclear inclusions seen on microscopy [18] and by a characteristic acute toxic renal lesion demonstrated by biopsy[19], there has never been any doubt that acute lead intoxication could induce a proximal tubular lesion. Intranuclear inclusion bodies could be produced predictably and regularly in experimental animals [20–23] and detailed study of the nature of these inclusions has shown them to contain both lead and protein [24]. Considerable controversy persisted, however, as to whether prolonged lead absorption and intoxication could produce a chronic renal lesion and result in the granular contracted kidneys which had been reported by the nineteenth century workers. Such a doubt was entirely reasonable because, as a disease, chronic lead nephropathy had virtually disappeared from most of the developed nations of the world, and these were the ones contributing most to the world's medical literature.

However, a group of physicians in Queensland, Australia, continued to see cases of chronic renal failure occurring many years after an episode of acute lead poisoning in childhood. They believed from their follow-up of such cases that the chronic renal lesion was etiologically associated with the earlier lead intoxication [25]. Queensland was in a somewhat unique situation in that it was a Western civilization which had developed in a tropical and subtropical location. For coolness, houses were built on 8 foot high stumps and were surrounded by wide open verandas, often with wooden railings, which were painted with the only paint available at that time—a paint based on lead pigments. Because it was both a safe and cool place to play, children frequently spent prolonged periods on these verandas and could easily ingest over a period large amounts of the lead paint which tended to powder and flake in the hot sun and come off on the hands. Thus, acute lead poisoning in childhood became a very common disease in Queensland in the late nineteenth and early twentieth centuries. Some twenty or more years later, a very high incidence of chronic renal failure with granular contracted kidneys was detected in Queensland, a rate which far exceeded that in the rest of Australia. Case follow-up at that time and a careful examination of possible etiological features led several investigators [26–29] to conclude that the increased incidence of chronic renal failure was a sequel to renal damage resulting from long and continued lead intoxication in childhood. This led the local medical association to recommend the exclusion of lead from paints in areas accessible to children and legislation to this effect was introduced in 1922, although it took some years for this legislation to have full effect. Subsequently, over a thirty year period, there was a steady decline in the mortality from renal failure in Queensland, until it approached that in the other Australian states.

Further evidence for a lead etiology in this chronic nephropathy was provided by a retrospective study of several aspects of the problem by Henderson [30–33]. Comparison of the mortality statistics in Queensland and other Australian states led to the conclusion that the excess mortality from chronic nephritis in Queensland was explicable by the action of a nephrotoxic agent which had affected Queensland children between 1870 and 1920, and which could initiate renal changes leading—in 10 to 40 years—to death from chronic nephritis [31]. In addition, an extensive follow-up of the mortality and incidence of

renal disease in over 400 persons who as children had been admitted to the hospital in Brisbane between 1915 and 1935 with a diagnosis of lead poisoning disclosed a great increase in mortality from renal and vascular disease. One hundred and sixty-five had died, 108 from chronic nephritis or hypertension; of the survivors, 17 had proteinuria and hypertension and three had hypertension alone [30]. In a later study, the lead content of bone was correlated with the renal histology in patients dying with granular contracted kidneys between 1952 and 1955, and this revealed that, whereas the renal pathology in almost two-thirds of the cases could not be ascribed to recognized causes, the lead content of bone in these subjects with cryptogenic nephritis was significantly greater than that in the other patients with a chronic nephropathy of recognized cause [32]. This latter finding led to acceptance of the hypothesis that an elevation in the lead content of bone is a prerequisite for the diagnosis of chronic lead nephropathy.

However, a similar follow-up of cases of acute lead poisoning in Boston and Baltimore [34, 35] failed to show a similar incidence of late chronic renal damage, although occasional cases similar to the Queensland patients were seen. Moreover, the US cases failed to show an increase in urinary lead after the administration of EDTA, a finding which led Chisholm [35] to conclude that lead absorption in the Queensland cases must have been of a much more prolonged variety, whereas that in the US cases would have been more acute. Many fascinating explanations for this discrepancy come to mind, but further studies to elucidate the precise reason have been precluded by the gradual disappearance of the disease in Queensland. However, it may be relevant that, in animal studies, the amount of lead absorbed and the degree of lead toxicity may be modified by a number of other factors, such as the level of dietary calcium [36], the presence of iron deficiency [37], the exposure to sunlight and the administration of Vitamin D

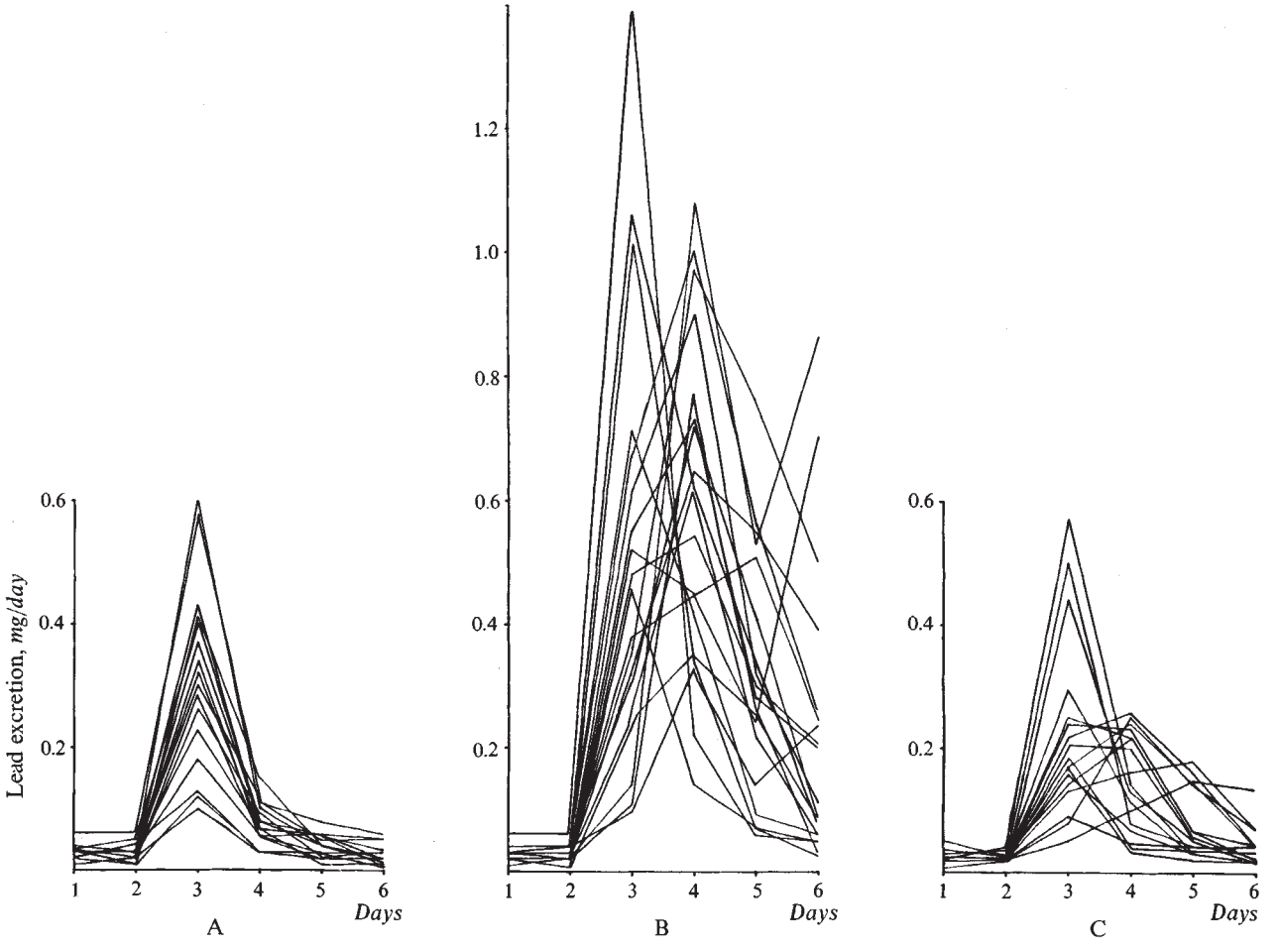

Fig. 1. *The alteration in urinary lead excretion after the administration of calcium EDTA on Day 3.* Group (A) were control subjects Group (B) were patients with chronic lead nephropathy; Group (C) were patients with chronic renal insufficiency attributable to causes other than childhood lead poisoning. This illustrates the prolongation of the EDTA-induced lead excretion by renal failure, the considerable increase in lead excretion after EDTA in chronic lead nephropathy and the normal lead excretion pattern after EDTA in renal disease not due to lead. [Modified from *Aust Ann Med* (1963) 12:316 and Emmerson [45] by permission of Blackwell Scientific Publications]

[38, 39]. These latter factors may explain the higher incidence of acute lead poisoning in the summer in USA.

The controversy over the association between prolonged lead exposure in man and the subsequent development of chronic renal disease might have been more easily resolved if a similar nephropathy could have been readily reproduced in animals. With a few exceptions [40], early studies failed to show the development of a chronic lesion, although the dose of lead given and its duration were clearly critical. However, focal scarring was seen in the remaining kidney when unilateral nephrectomy was performed after the administration of lead [41], and more recent study of the problem by Goyer [42] has shown that the prolonged administration of lead to rats predictably results in both tubular atrophy and interstitial scarring, the morphological appearances being similar to those seen in the kidneys of persons with excessive past lead absorption.

In order to study renal function in the Queensland cases, attempts at diagnosis of chronic lead nephropathy during life were made [43] and the following criteria were suggested as a basis for clinical diagnosis: 1) features of a long-standing, slowly progressive chronic renal disease, 2) a moderate to considerable degree of uniform contraction of both kidneys, 3) definite evidence of excessive past lead absorption and 4) the exclusion of alternative causes for chronic renal disease. A comparison of the urinary excretion of lead after a standard infusion of calcium EDTA revealed that a significantly greater increase in urinary lead excretion occurred in subjects who had had lead poisoning in childhood and who exhibited the other criteria for a diagnosis of chronic lead nephropathy than in subjects without such a history or subjects with renal disease due to causes other than lead (Fig. 1) [44]. It appeared that the processes of renal failure had resulted in the mobilization of lead from bone where it had remained since the episode of acute lead poisoning and that an increased amount of tissue lead was thereby made accessible to the chelating agent. The pathological appearance of the Queensland kidneys is characteristic but not pathognomonic, the essential feature being a reduction in the number of functioning nephrons, with hypertrophy of the remaining nephrons, and considerable contraction and interstitial fibrosis (Fig. 2) [45]. The appearance is that of a kidney in which nephrons have been destroyed and have subsequently disappeared without trace.

Chronic lead nephropathy also came to be recognized in other parts of the world. It was thought to be common in lead workers in France [46] and Richet et al [47] described details of the findings in the kidneys of eight Parisians who demonstrated evidence of both low grade lead intoxication

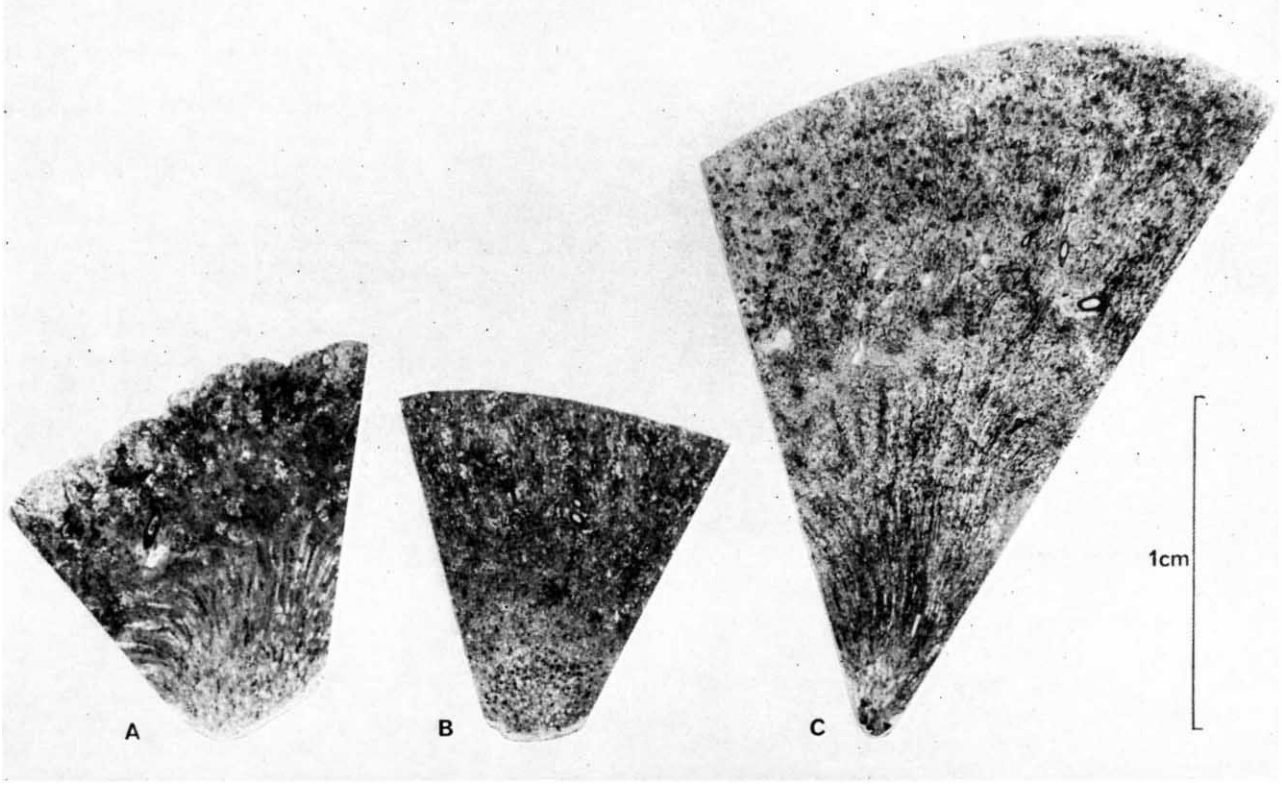

Fig. 2. *A comparison between sections taken from cortex to papilla in the kidneys of (A) chronic lead nephropathy, (B) chronic glomerulonephritis and (C) a normal kidney (PAS stain × 3).* The lead nephritic kidney shows coarse granularity with gross cortical atrophy and interstitial fibrosis. The glomerulonephritic kidney shows large numbers of glomerular remnants, a uniform pattern of involvement and moderate cortical atrophy. [From Emmerson, 1967 [45] by permission of Blackwell Scientific Publications]

and a chronic renal lesion. These patients differed from the Queensland patients in that their lead contact was a continuing one and lead toxicity had persisted, with intranuclear inclusion bodies in renal tubular cells. Additional reports of renal function and structure in chronic lead nephropathy were published from Italy [48, 49], Rumania [10, 50] and Yugoslavia [11, 51]. A remarkable similarity to the picture of chronic lead nephropathy was also seen in the nephropathy of "moonshine"[1] drinkers in the southern states of the USA [52, 53]. These subjects showed a pattern of chronic renal failure with a protracted course and contracted kidneys. Clear evidence of persistent lead intoxication, including intranuclear inclusion bodies in renal epithelial cells, could usually be found. As the moonshine contained many other possible nephrotoxins, lead could not be proved to be the cause, but comparison with cases of lead nephropathy elsewhere in the world suggested that it was. The renal pathology was remarkably similar to that seen in the Queensland cases of chronic lead nephropathy, a diagnostic infusion of calcium EDTA provided evidence of excessive lead storage in these subjects [54] and other sensitive parameters of lead intoxication were positive [55].

Another aspect of similarity between these cases and those in Australia (as well as with the cases of chronic lead intoxication described in the nineteenth century) was the frequent association with gout. Emmerson [44] recorded that 50 percent of his cases with chronic lead nephropathy had, at one time or another, suffered from acute gouty arthritis and that, unlike primary gout, this incidence was the same in females as in males. Subsequent investigation revealed that the disproportionate hyperuricemia of chronic lead nephropathy in Queensland was due to a defect in renal excretion of urate [43], an opinion originally proposed by Garrod in 1876 [56]. Studies of urate kinetics in moonshine drinkers with gout [57] also confirmed a renal pathogenesis for the hyperuricemia of that condition. Subsequent attempts to determine the relative contribution of tubular reabsorption and secretion to this reduction in urate excretion have, within the limitations determined by the interpretation of alterations in urate excretion following pyrazinamide, suggested the presence of excessive tubular reabsorption of urate as the cause for the undue hyperuricemia in lead nephropathy [58]. The implications from this finding that there may be a reduced circulating plasma volume in these subjects has not been followed further because of the paucity of surviving subjects with lead nephropathy. However, it would be consistent with the suggestion [59] that lead may also have an effect upon the renin-angiotensin-aldosterone system.

None of these studies individually can be said to provide conclusive proof of an etiological relationship between prolonged lead absorption and chronic renal disease. The combined evidence, however, is such as to make a cause and effect relationship highly likely. It would seem that little more can be done to establish further this relationship in man, except that an awareness of the possibility of chronic lead nephropathy and an appropriate search for it in suitable cases, either by the measurement of the lead content of bone [60] or the urinary lead excretion following an EDTA infusion [44], may lead to the establishment of this diagnosis in cases of otherwise undiagnosable chronic renal disease.

[1] Illicitly distilled liquor.

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